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09/064,000	04/21/1998	JAMES P. ELIA	796-P-12	5311

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/064,000	**Applicant(s)** ELIA, JAMES P.	
	Examiner Elizabeth C. Kemmerer, Ph.D.	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 02 December 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *382-394*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: please see attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: Please note attached Notice of References cited.

ATTACHMENT TO THE ADVISORY ACTION

In view of the after-final status of the application, only substantially new arguments and evidence will be addressed.

35 U.S.C. § 112, Second Paragraph

Claims 383, 384, 391, 393, and 394 remain rejected undr 35 U.S.C. § 112, second paragraph, for reasons of record.

Applicant relies on a bio.com referece as evidence of the exisntece of pluripotent cells which are not stem cells. This has ben fully considered but is not found to eb persuasive. The bio.com reference states, "...despite their remarkable similarities to embryonic stem cells, amniotic epithelial cells are not stem cells *per se.*" The bio.com reference is a summary of a full-length research paper by Miki et al. (2005, Stem Cells 23:1549-1559) who clearly state in their abstract that "Amnion derived from term placenta after live birth may be a useful and noncontroversial source of *stem cells* for cell transplantation and regenerative medicine." Furthermore, Miki et al. was published well after the filing date, and thus the skilled artisan would not have known of any pluripotent cells other than stem cells. The specification does not disclose such.

Applicant presents references describing unipotent stem cells. This has been fully considered but is not found to be pereuasive. The references relied upon by Applicant were all published well after the filing date. Therefore, the evidence is not inconsistent with the skilled artisan's understanding of "stem cells" at the time fo the invention. Furthermore, Applicant states in the instant response that unipotent stem

cells are not considered to be part of the inventin (p. 13). Therefore, the issue is not relevant.

Applciatn argues that "multifactorial and non-specific" is used in the instant specification with reference to cells. This is not found to be persuasive, since the instant specification does not provide a clear definition of the term with regard to cells for reasons of record. The prior art also does not provide a clear definition. Therefore, at the time of the invention, the skilled arisan would not have been able to determine the metes and bounds of the claime divention. Since the term "multifactorial and non-specific cells" is not used in the prior art, the skilled artisan must look to the specification for a definition. Page 37 of the specification states, "Multifactorial and nonspecific cells (**such as** stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated" (emphasis added). The use of "such as" clearly implies that the term "multifactorial and non-specific cells" is intended to encompass cells other than stem cells and germinal cells. However, neither the specification nor the art disclose what these other cells are. In the absence of this information, the skilled artisan cannot determine the metes and bounds of the claims at issue. The functional portion of the definition, "...provide[s] the necessary in vivo and in vitro cascade of genetic material ..." makes no sense. What is a cascade of genetic material? Neither the specification nor the art clearly define these terms. Regarding p. 48 of the specification, the term at issue "multifactorial and non-specific cell" is not mentioned. Regarding p. 50, the addition of the term "pluripotent" does not resolve the indefiniteness. Stem cells are

known in the art to be pluripotent; however, it is unclear what other cell types are considered by Appellant to be pluripotent.

Citing case law, Applciant argues that the examiner should interpret "multifactorial" and"non-specifc" in light of the specificaiton as such would be apparent to a person skille din the medical art. Applicant argues that a non-contextual interpretation, suh as that foisted by the examiner would not have the same evidentiary weight. This has been fully considered but is not fund to be persuasive. There is no evidene that a skilled artisan would understand "multifactorial" and "non-specific" as it realtes to a description of cells, for reasons of record. The examiner has provided publications in support of this rejection.

Applciant argues that the examiner is relying upon an abswence of results in a search regarding these terms, and that such does not constitute evidence. Applicant urges that the examiner has improperly interpreted the word "factor" as a chemist rather than a medical professional. Applicant urges that one skilled in the medical art would have no trouble understanding this term. This has been fully considered but is not found to eb persuasive. At no point did the examiner indicate that anything was being evaluated from the perspective of a chemist. Applciant has provided no eviedne that a skilled person in the medical art would assign any particular meaning to the term at issue. For example, Applciant has provided no publications from the relevant art that use the term with regard to cells.

Applicant indicates that the fifth supplemental information disclosure statemenet lists relevant search evidence. This has been fully considered but is not foun to be

persausvie. The fifth IDS provides dictionary definitions of "multifactorial" and "nonspecific" but does not use them to describe cells. Regarding the dictionary definitions, the dictionary.net's definition of multifactorial is "involving or depending on several factors or causes (especially pertaining to a condition or disease resulting from the interaction of many genes)." This supports the rejection in that the term "multifactorial" is not used to describe cells. It is used to describe a cause (for example, of the disease) or an effect (for example, of the genes). Similarly, the dictionary.net's definition of nonspecific is "not caused by a specific agent; used also of staining in making microscope slides; 'nonspecific enteritis'" supports the rejection. "Nonspecific" is not used to describe cells. How can cells be "not caused by a specific agent?" The definition uses the term to describe causes (i.e., nonspecific enteritis is a disease caused by undefined factors).

Applicant provides dictionary definitions of "factor" and "multifactorial." Applicant argues that "factor" can be a cell, and cells are multifatorial when more than one factor promote the growth of soft tissue. This has been fully considered but is not found to be persuasive. If "factor" can mean a cell, wouldn't "multifactorial" mean several cells? The connection to soft tissue effects is not clear.

Applicant refers to the second supplemental declarations of Drs. Heuser and Lorincz. The second supplemental declarations of Drs. Heuser and Lorincz are insufficient to overcome the rejection of claims 383, 384, 391, 393, and 394 based upon 35 U.S.C. § 112, second paragraph because, although the declarations use the term "multifactorial and non-specific cells," they do not explain what cells are encompassed

by the term. See section 7 of each of the Heuser and Lorincz second supplemental declarations. In view of the totality of the evidence of record, which includes the specification, prior art of record, and declarations submitted under 37 CFR 1.132, an unambiguous definition of the term "multifactorial and non-specific cells" has not been provided. Therefore, the skilled artisan would have been unable to determine the metes and bounds of the claims.

Applicant points to Strauer 2005 as stating that the regenerative potential of bone marrow derived stem cells may be explained by any of four mechanisms, and that "mechanisms" are further referred to as "factors." Applicant argues that the cells can be described as four-factor cells, i.e., multifactorial. Applicant concludes that the totality of the evidence indicates that the rejection should be withdrawn. Applicant also argues that "non-specific" is synonymous with "non-specialized." This has been fully considered but is not found to be persuasive. Strauer 2005 uses "four mechanisms" to describe "regenerative potential," not the cells *per se*. Even if Strauer 2005 could be tortuously construed as describing bone marrow stem cells as multifactorial, Strauer 2005 only discusses bone marrow stem cells. The specification already indicates that stem cells are exemplary of "multifactorial and non-specific" cells. The issue is what cells other than stem cells and germinal cells can be considered multifactorial and non-specific, given that the art does not apply these terms to cells.

Applicant refers to Caplan et al. (2001, Trends Mol. Med. 6:259-264) to support their position. This has been fully considered but is not found to be persuasive. Caplan

et al. use the word "multifactorial" to describe the *process* of differentiation pathway, thus supporting the examiner's position.

Applicant argues that their position is supported with evidence, and the examiner's is not. This has been fully considered but is not found to be persuasive. The examiner's position is supported by Strauer 2005, Caplan, and the dictionary definitions of record.

Applicant urgesd that there can be no question as to the meaning of "multifactorial" and that "non-specific" means "non-specialized." However, this is unsupported by evidence for reasons of record.

Applicant argues that the examiner is incorrect regarding the contradictory nature fo the claims. This has been fully considered but is not found to be persuasive. The fact that the claim dependencies specifically indicate that stem cells are a narrower sub-genus than multifactorial and nonspecific cells (re: claims 383 and 384) AND vice versa (re: claims 393 and 394), is inherently contradictory.

In conclusion, the term "multifactorial and non-specific cells," recited in the claims, is not defined unambiguously in the prior art or in the specification, for the reasons set forth above. Therefore, the skilled artisan cannot determine the metes and bounds of the claimed invention, and the rejection is proper.

35 U.S.C. § 102

Claims 382-394 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Lutjen et al. for reasons of record.

Applicant argues that the examiner has incorrectly interpreted "integrating" as recited in the claims and intended by Applicant. Applicant argues that the claims must be read in light of the specification. Applicant points to the specification as implying that the new soft tissue is permanently integrated into the patient's body. This has been fully considered but is not found to be persuasive. Limitations from the specification are not to be read into the claims. The word "integrating" is not a technical term, rather, it is a plain English word. The tissues involved in a pregnancy are integrated into the body of the mother. The conceptus implants itself into the lining of the mother's uterus such that the maternal epithelial cells completely envelop the conceptus, thus integrating the conceptus in the body of the mother. This is known as invasive implantation, and it occurs in humans. Such is well known in the medical art. See the textbook Essential Reproduction (2000, fifth edition, Johnson and Everitt, eds., Blackwell Science, pp. 177-180, esp. p. 178, right column). See also Stedman's Medical Dictionary definition of placenta (cited in the previous Office Action, which states that a placenta is an

> "organ of metabolic interchange between fetus and mother. It has a **portion of embryonic origin**, derived from a highly developed area of the outermost embryonic membrane (chorion frondosum), **and a maternal portion** formed by a modification of the part of the uterine mucosa (decidua basalis) in which the chorionic vesicle is **implanted**." (emphasis added)

Furthermore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., permanent integration) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read

into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that the Stedman's Medical Dictionary definition of placenta supports Applicant's position, in that it states that there is no mixing of fetal and maternal blood, and that improper integration events (such as percreta or ectopic pregnancy) result in catastrophic events. Applicant argues that Lutjen et al. did not report any harmful integration, since a healthy baby was born. This has been fully considered but is not found to be persuasive. There need not be mixing of blood for integration. Stedman's Medical Dictionary definition of placenta indicates that it is an organ made of embryonic and maternal portions. At no point do these portions separate from one another, even at birth. Humans experience invasive implantation of a conceptus. Thus, integration has occurred.

Applicant takes issue with the examiner's statement that none of the claims exclude totipotent cells in that the claims require a class of cells that induce the growth of soft tissue which integrates with the patient's body. Applicant urges that unipotent or totipotent cells are incapable of growing and integrating an artery in the patient's body and are therefore excluded from the claims. Applicant argues that the examiner's attempt to hold the claim language indefinite and at the same time anticipated by Lutjen to be derogating to the record and current law. This has been fully considered but is not found to be persuasive. The cells implanted by Lutjen et al. induced the growth of soft tissue, including arteries. The claims recite open claim language and thus do not require exclusion of the growth of hard tissues. Finally, the rejections under 35 U.S.C.

§§ 112, second paragraph, and 102(b) are not contradictory. Examiners are instructed to examine each claim for compliance with each statute and rule, thereby avoiding piecemeal examination. See M.P.E.P § 704.01. Thus, while a claim may raise issues of indefiniteness necessitating a rejection under 35 U.S.C. § 112, second paragraph, the same claim still must be examined with respect to whether or not it reads on the prior art. In this situation, the M.P.E.P. instructs the examiner to give the claim its broadest reasonable interpretation, and apply art in rejections under 35 U.S.C. §§ 102 and 103 as appropriate. Therefore, both rejections under 35 U.S.C. §§ 112, second paragraph, and 102 are deemed appropriate.

Applicant argues that totipotent cells are not stem cells, relying on "Stem Cells: A Primer." Applicant urges that totipotent stem cells do not have the ability to self-renew *in vitro* indefinitely, that pluripotent cells do not form a placenta, and that embryonic stem cells do not develop into a fetus. Applicant urges that there is no evidence that embryonic stem cells are totipotent. Applicant argues that Lutjen's cells do not grow and integrate desired soft tissue as do the multifactorial and non-specific cells of claim 383, the stem cells of claims 384, 389, and 393, and the pluripotent cells of claim 391. Applicant argues that the claims and specification do not describe using a two-celled embryo and that the invention would not be operative using such. Applicant argues that the recitation "growing and integrating said desired soft tissue in said body of said human patient" precludes formation of a placenta and fetus. This has been fully considered but is not found to be persuasive. The cells used by Lutjen et al. clearly integrate in the body of the human patient in that all human pregnancies proceed via

invasive implantation wherein the maternal cells completely envelop the fetus. This is an integration event. Also, the cells of Lutjen et al. form desired soft tissue, including artery, in the body of the human patient. Since the cells of Lutjen et al. give rise to each cell type in the developing fetus, clearly they are stem cells. The claims do not require exclusion of placenta formation, due to the use of open claim language. Lutjen et al. teach each method step of each claim, and thus anticipates each claim.

Applicant argues that the examiner has mischaracterized Fukuda et al. This has been fully considered but is not found to be persuasive. At p. 1275, Fukuda et al. remarks that application of BIO causes ES cells to remain pluripotent. This is not to say that ES cells are not totipotent. At p. 1273, Fukuda et al. state that ES cells have the ability to differentiate into any cell type of any organ. Such is the definition of totipotent. See also Colombo et al. (published online December 9, 2005, Stem Cells Express) who describe embryonic stem cells as totipotent (p. 2).

Applicant takes issue with the examiner's reliance on Satoh et al. This has been fully considered but is not found to be persuasive. Regarding Applicant's statement that pluripotent cells can promote the growth of all three major soft tissue types, this definition is also not consistent with the use of "pluripotent" by the art. For example, Satoh et al. (2005, Leukemia (in press)) discusses myeloid-restricted hematopoietic stem cells and lymphoid-restricted hematopoietic stem cells (see Fig. 1). Such *pluripotent* stem cells are capable of differentiating into more than one cell type, but are not capable of differentiating into *all three* major soft tissue types.

Applicant takes issue with the examiner's reliance on Alberts et al., stating that her reasoning is bogus. This has been fully considered but is not found to be persuasive. The reference to Alberts et al. was made to address Applicant's mischaracterization of totipotent cells as the "master cells" of the body *because they contain all the genetic information needed to create all the cells of the human body.* This is factually incorrect. Almost all human cells having a nucleus and mitochondria contain all of the genetic information needed to create all the cells of the human body plus the placenta, because *they all contain the identical genome, i.e., all the genetic information needed to create all the cells of the human body.* What determines whether a cell is a neuron or a keratinocyte or a hematopoietic cell or a totipotent stem cell or any cell type is the *control* of expression of the genome. See Alberts et al., eds., 1983, Molecular Biology of the Cell, Garland Publishing, Inc., New York, pp. 23-26.

Applicant urges that Dr. Elia has maintained that the disclosure and claims do not include use of totipotent cells since such cells would not provide the claimed desired therapeutic effect. The claims do not exclude totipotent cells. The specification does not teach exclusion of totipotent cells.

For all of these reasons, the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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ECK

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER